Draft Guidance on Azelaic Acid

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Azelaic acid

Dosage Form; Route: Aerosol foam; topical

Recommended Studies: One study

In Vivo Study:

- Type of study: Clinical endpoint bioequivalence study
- Design: Randomized, double blind, parallel, placebo-controlled in vivo
- Strength: 15%
- Subjects: Males and females with rosacea.
- Additional comments: Specific recommendations are provided below.

Analytes to measure (in appropriate biological fluid): Not applicable.

Bioequivalence based on (90% CI): Clinical endpoint.

Waiver request of in vivo testing: Not applicable.

Dissolution test method and sampling times: Not applicable.

Additional comments regarding the clinical endpoint bioequivalence study:

1. The Office of Generic Drugs (OGD) recommends a clinical endpoint bioequivalence study in the treatment of moderate rosacea. Subjects are to be randomized to receive the generic Azelaic Acid topical foam, 15%, the reference listed drug (RLD), or placebo twice daily for 12 weeks. The primary endpoint is to be evaluated at the end of treatment (study Week 12).

2. Inclusion Criteria (the sponsor may add additional criteria):
   a. Healthy male or nonpregnant female aged ≥ 18 years with a clinical diagnosis of moderate facial rosacea, defined as the presence of:
      i. At least eight and not more than fifty inflammatory facial lesions (i.e., papules/pustules), AND
      ii. Persistent erythema, AND
      iii. Telangiectasia.
b. Subject willing to minimize external factors that might trigger rosacea flare-ups (e.g., spicy foods, thermally hot foods and drinks, hot environments, prolonged sun exposure, strong winds and alcoholic beverages).

3. Exclusion Criteria (the sponsor may add additional criteria):
   a. Pregnant or lactating or planning to become pregnant during the study period.
   b. Presence of any skin condition on the face that would interfere with the diagnosis or assessment of rosacea.
   c. Excessive facial hair (e.g. beards, sideburns, moustaches, etc.) that would interfere with diagnosis or assessment of rosacea.
   d. History of hypersensitivity or allergy to propylene glycol or any other component of the formulation.
   e. Use within 6 months prior to baseline of oral retinoids (e.g. Accutane®) or therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed).
   f. Use for less than 3 months prior to baseline of estrogens or oral contraceptives; use of such therapy must remain constant throughout the study.
   g. Use within 1 month prior to baseline of 1) topical retinoids to the face, 2) systemic antibiotics known to have an impact on the severity of facial rosacea (e.g., containing tetracycline and its derivatives, erythromycin and its derivatives, sulfamethoxazole, or trimethoprim), or 3) systemic corticosteroids.
   h. Use within 2 weeks prior to baseline of 1) topical corticosteroids, 2) topical antibiotics or 3) topical medications for rosacea (e.g., metronidazole, azelaic acid).
   i. Subjects with moderate or severe rhinophyma, dense telangiectases, or plaque-like facial edema.
   j. Ocular rosacea (e.g., conjunctivitis, blepharitis, or keratitis) of sufficient severity to require topical or systemic antibiotics.

4. The protocol should include a list of the prescription and over-the-counter drug products that are prohibited during the study, such as:
   a. Any other topical products applied to the target site (e.g., metronidazole, topical antibiotics, topical steroids).
   b. Oral retinoids.
   c. Systemic (e.g., oral or injectable) antibiotics known to have an impact on the severity of facial rosacea (e.g., containing tetracycline, erythromycin, sulfamethoxazole, or trimethoprim or their derivatives).
   d. Systemic corticosteroid or immunosuppressive drugs.
   e. Antipruritics, including antihistamines, within 24 hours of study visits.

5. Subjects should not apply moisturizers, new brands of make-up, creams, lotions, powders or any topical product other than the assigned treatment to the treatment area. Occlusive dressings or wrappings should be avoided in treatment areas. Subjects should minimize exposure to sunlight, including sunlamps, while using the product. Use of sunscreen products and protective clothing over treated areas is recommended when sun exposure cannot be avoided.
6. Areas to be treated should be washed with a mild cleanser before application and patted dry with a soft towel. A thin layer of study treatment should be applied to the entire facial area (cheeks, chin, forehead, and nose) twice daily, in the morning and evening, for 12 weeks. Contact with the mouth, eyes and other mucous membranes should be avoided. The hands should be washed following application.

7. The recommended primary endpoint of the study is the mean percent change from baseline to week 12 in the inflammatory (papules and pustules) lesion counts. The protocol should clearly define papules, pustules, and nodules. When counting facial lesions, it is important that all lesions be counted, including those present on the nose. Counts of nodules should be reported separately and not included in the inflammatory lesion counts.

8. An Investigator’s Global Evaluation (IGE) should be evaluated as a secondary endpoint for the statistical analysis. The IGE should be a static scale, describing the extent of disease associated with each score. This scale should not reflect treatment response, but should describe the condition at each visit. Therefore, no reference should be made to baseline in the evaluation. The scale should be dichotomized into "success" and "failure". "Success" should be defined either as a score consistent with clear or almost clear at the final visit.

<table>
<thead>
<tr>
<th>Score</th>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Clear</td>
<td>No inflammatory lesions present; at most, mild erythema</td>
</tr>
<tr>
<td>1</td>
<td>Almost Clear</td>
<td>Very mild erythema present. Very few small papules/pustules</td>
</tr>
<tr>
<td>2</td>
<td>Mild</td>
<td>Mild erythema. Several small papules/pustules</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>Moderate erythema. Several small or large papules/pustules, and up to 2 nodules</td>
</tr>
<tr>
<td>4</td>
<td>Severe</td>
<td>Severe erythema. Numerous small and/or large papules/pustules, up to several nodules</td>
</tr>
</tbody>
</table>

9. The protocol should clearly define the Per-Protocol (PP), modified Intent-To-Treat (mITT) and safety populations.
   a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who:
      i. Meet all inclusion/exclusion criteria
      ii. Are dosed a pre-specified proportion of the scheduled doses (Generally At least 75% and no more than 125%) of the assigned product for the specified duration of the study. The protocol should specify how compliance will be verified, (e.g., using subject diaries).
      iii. Do not miss a pre-specified number of scheduled doses for more than pre-specified number of consecutive days.
      iv. Complete the evaluation within the designated visit window with no protocol violations that would affect the treatment evaluation.
   b. The mITT and safety populations include all randomized subjects who use at least one dose of product.

10. Subjects who are discontinued early from the study due to lack of treatment effect should be included in the PP population using Last Observation Carried Forward (LOCF).
whose condition worsens and who require alternate or supplemental therapy for the treatment of their condition during the treatment phase of the study should be discontinued, included in the mITT and PP population analyses using LOCF, and provided with effective treatment. Subjects discontinued early for other reasons should be excluded from the PP population, but included in the mITT population, using LOCF. Applicants should provide a pre-specified definition of lack of treatment effect.

11. The start and stop calendar date (e.g., mm/dd/yyyy) and study day (e.g. Day X) of concomitant medication use should be provided in the data set in addition to the reason for the medication use. The Applicant should clearly note whether the medication was used prior to baseline visit, during the study, or both.

12. If the study allows for the use of a rescue medication, the Applicant should submit a data set that includes the date and time of each rescue medication use for each subject who used the rescue medication at any point during the study. The Applicant should pre-specify rescue medication use (name, type, amount, frequency, reason to use), maximum allowable amount of daily rescue medication use, and any limitations (e.g., cannot use rescue medication within pre-specified number of hours prior to primary endpoint evaluation) for rescue medication use during the study.

13. All Adverse Events (AEs) should be reported, regardless of their relation to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome and date of resolution. This information is needed to determine if the incidence and severity of adverse reactions is different between the test product and RLD.

14. All pregnancies should be reported, including outcome information.

15. It is the Applicant's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.

16. A placebo control arm is recommended to demonstrate that the test product and RLD are active and as a parameter that the study is sufficiently sensitive to detect differences between products.

17. To establish bioequivalence for a dichotomous endpoint, it is recommended the following compound hypotheses be tested using the per protocol population:

\[ H_0: \pi_T - \pi_R < \Delta_1 \text{ or } \pi_T - \pi_R > \Delta_2 \text{ versus } H_A: \Delta_1 \leq \pi_T - \pi_R \leq \Delta_2 \]

where \( \pi_T \) = the success rate of the primary endpoint for the treatment group, and \( \pi_R \) = the success rate of the primary endpoint for the reference group.

The null hypothesis, \( H_0 \), is rejected with a type I error (\( \alpha \)) of 0.05 (two one-sided tests) if the estimated 90% confidence interval for the difference of the success rates between test and reference products (\( \pi_T - \pi_R \)) is contained within the interval \([\Delta_1, \Delta_2]\), where \( \Delta_1 = -0.20 \) and
\[ \Delta_2 = 0.20. \text{ Rejection of the null hypothesis supports the conclusion of equivalence of the two products.} \]

To establish bioequivalence for a continuous endpoint, it is recommended the following compound hypotheses be tested using the per protocol population:

\[ H_0: \frac{\mu_T}{\mu_R} < \theta_1 \text{ or } \frac{\mu_T}{\mu_R} > \theta_2 \text{ versus } H_A: \theta_1 \leq \frac{\mu_T}{\mu_R} \leq \theta_2 \]

where \( \mu_T \) = mean of the primary endpoint for the test group, and 
\( \mu_R \) = mean of the primary endpoint for the reference group

The null hypothesis, \( H_0 \), is rejected with a type I error (\( \alpha \)) of 0.05 (two one-sided tests) if the estimated 90% confidence interval for the ratio of the means between test and reference products \( \frac{\mu_T}{\mu_R} \) is contained within the interval \([\theta_1, \theta_2]\), where \( \theta_1 = 0.80 \) and \( \theta_2 = 1.25 \). Rejection of the null hypothesis supports the conclusion of equivalence of the two products.

18. To establish sensitivity within the study for either a dichotomous or continuous primary endpoint, the test and reference products should both be statistically superior to the placebo. Conduct an appropriate two-sided inferential test with a type I error (\( \alpha \)) of 0.05, using the mITT population.

19. The study data should be submitted in standardized format. Please refer to study data standards published at www.FDA.gov\(^1\).

20. The protocol should include a section with fully detailed statistical analysis plan.

21. Please provide the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
   a. Study identifier
   b. Unique subject identifier
   c. Subject identifier for the study
   d. Study site identifier (if applicable)
   e. Age
   f. Age units (years)
   g. Sex
   h. Race
   i. Name of planned treatment
   j. Name of actual treatment
   k. Safety population flag (yes/no)
   l. Reason for exclusion from safety population
   m. Modified Intent-to-Treat (mITT) population flag (yes/no)
   n. Reason for exclusion from mITT population
   o. Per-Protocol (PP) population flag (yes/no)

\(^1\) Study Data Standards for Submission to CDER available at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/uc
m248635.htm
p. Reason for exclusion from PP population
q. Randomized population flag (yes/no)
r. Date/time of first exposure to treatment
s. Date/time of last exposure to treatment
t. End of study date
u. End of study status
v. Subject required additional treatment due to unsatisfactory treatment response (yes/no)
w. Baseline lesion count (papules and pustules)
x. Week 12 lesion count (papules and pustules)
y. Compliance rate (%)
z. Subject missed the pre-specified number of scheduled doses for more than pre-specified number of consecutive days (yes/no)
aa. Adverse event reported (yes/no)
bb. Concomitant medication (yes/no)

22. Please provide the basic data structure (BDS) dataset with records per subject, per visit, per analysis timepoint, using the following headings, if applicable:
a. Study identifier
b. Unique subject identifier
c. Subject identifier for the study
d. Study site identifier (if applicable)
e. Name of planned treatment
f. Name of actual treatment
g. Safety population flag (yes/no)
h. Modified ITT population flag (yes/no)
i. Per-Protocol (PP) population flag (yes/no)
j. Analysis date
k. Analysis visit
l. Study visit within the designated window (yes/no)
m. Analysis timepoint (e.g., hour 0, hour 2) (if applicable)
n. Papule count
o. Pustule count
p. Nodule count
q. Erythema score
r. IGE score
s. Additional treatment required during the visit (yes/no)
t. Adverse event reported during the visit (yes/no)
u. Concomitant medication during the visit (yes/no)